OFFICE OF THE DIRECTOR

The Office of the Director (OD), NIAID, provides policy guidance, program development and evaluation, and overall operational and administrative coordination for the Institute. OD is the focal point of relationships with the Director of the NIH as well as with other components of the Department of Health and Human Services (DHHS), other Federal agencies, Congress, professional societies, voluntary health organizations, and other public groups. The activities of OD also include advising and guiding NIAID's key leaders on the principles, practices, laws, regulations, and policies of the Federal equal employment, affirmative action, civil rights, and minority programs. Offices within OD provide critical management and administrative support to the Institute. By carrying out their individual tasks, OD offices play a key role in helping the Institute achieve its mission. Brief descriptions of OD offices follow.

The Office of Administrative Services (OAS) assists NIAID staff in carrying out their responsibilities by providing administrative and acquisition management support services. These services include procurement, space management, and travel. OAS also develops internal controls in areas such as property accountability and financial monitoring, and coordinates and analyzes organizational changes.

The Office of Clinical Research manages and coordinates those NIAID research programs conducted at the Warren Grant Magnuson Clinical Center located on the NIH Bethesda campus. The Office promotes interactions and collaborations between intramural and extramural investigators and oversees NIAID's Institutional Review Board to provide initial and continuing review of intramural clinical research protocols to protect the welfare of human subjects recruited to participate in biomedical or behavioral research. The Office also provides relevant information from NIAID's intramural clinical research programs to the NIH community and other Government agencies, as well as to public and private organizations.

The Office of Communications and Public Liaison (OCPL) enables NIAID to meet an important part of its mission by conveying the goals and results of its research programs to health professionals, the news media, and the public. In addition to responding to more than 10,000 requests for information annually, the Office plans educational and media campaigns; develops and disseminates brochures, fact sheets, news releases, and audiovisual products; and produces educational exhibits for national and regional meetings. OCPL also coordinates NIAID's Web site activities.

The Office of Equal Employment Opportunity is responsible for planning, implementing, evaluating, and monitoring programs and initiatives to increase the number of minorities, women, and persons with disabilities in all scientific and administrative areas of the Institute. The Office also develops initiatives that further enhance biomedical research programs at historically black colleges and universities and at Hispanic-serving institutions, and coordinates all activities to implement NIH minority-assistance programs and objectives relevant to the mission of NIAID.

The Office of Ethics provides advice regarding conflict of interest of individuals involved in the conduct of biomedical research, including Government employees, advisory committee members, and non-government employees such as peer reviewers and Data Safety Monitoring Board members. The Office also administers a comprehensive NIAID ethics program that reflects statutory responsibilities and integrity in service to the public.

The Office of Financial Management provides overall financial planning, management, and budget analysis to the Institute Director and all NIAID components and provides budget-related materials for the NIAID Director's briefings with DHHS, the NIH Director, the Office of Management and Budget, and Congress.

The Office of Global Affairs (OGA) provides overall coordination of NIAID international activities through a matrix of international liaisons; it accomplishes its work with other NIH components and DHHS agencies through the Fogarty International Center. OGA also meets and greets international visitors and delegations, coordinates NIAID participation in bilateral and multilateral programs, negotiates and provides administrative support for the long-term assignment of NIAID staff and representatives overseas, and supervises the OGA/NIAID Epidemiology Group in support of intramural and extramural international projects.

The Human Resources Operations Branch C (NIAID), Division of Human Resources Operations, Office of Human Resources, NIH, provides human resource services for the Institute management, employees, and applicants. These services encompass recruitment and staffing, position management and classification, pay and compensation, employee relations, employee benefits, employee development, and advisory services.

The Office of Management for New Initiatives (OMNI) is responsible for managing the establishment of key resources for new NIAID scientific and administrative initiatives. OMNI also is charged with acquiring and developing physical, human, and contractual infrastructure to fulfill new and expanded NIAID mission requirements.

The Office of Policy Analysis provides support and serves as liaison to program managers to coordinate, integrate, and articulate long-range program goals and strategies; develop and coordinate the Institute's annual planning and reporting process; advise on material for all stages related to congressional budget presentations; direct and coordinate the legislative liaison, tracking, and analysis for the Institute; manage the Executive Secretariat function; direct and coordinate Freedom of Information Act (FOIA) activities; provide the secretariat function for selected advisory groups, such as the NIAID Executive Committee; prepare the NIAID Director for meetings with various constituency groups; and brief the NIAID Director in preparation for trans-NIH policy meetings.

The Office of Technology Development (OTD) supports NIAID's intramural and extramural research programs by facilitating collaborations between NIAID researchers and external research and development organizations. OTD's staff uses scientific, legal, and business expertise to negotiate

agreements with universities, small biotechnology companies, large national and multinational pharmaceutical concerns, and other government institutions. OTD manages NIAID's portfolio of patents and inventions and serves as NIAID's resource for all issues concerning intellectual property. OTD also manages the receipt of Cooperative Research and Development Agreement (CRADA) funds, supports the NIH's licensing program, and tracks license royalty receipts. In addition, OTD provides NIAID investigators with training on NIH technology transfer policies and regulations and guidance on conflict-of-interest issues.

The Office of Technology Information Systems (OTIS) manages technologies supporting NIAID biomedical research programs. The Office provides a spectrum of management, technologies development, applications/software engineering, bioinformatics support, and professional development. OTIS works closely with NIAID intramural, extramural, and administrative staff to provide technical support, liaison, coordination, and consultation on a wide variety of ventures. These projects and initiatives are aimed at ensuring ever-increasing interchange and dissemination of scientific information within the Federal Government and among the worldwide scientific network of biomedical researchers.

OUTREACH ACTIVITIES

The NIAID Office of Communications and Public Liaison (OCPL) is the focal point within the Institute for disseminating research results to the media, health professionals, and the public. An important part of NIAID's mission, this activity includes producing and disseminating print, audiovisual, and Web-based materials; distributing materials at professional and community meetings; and sponsoring workshops and conferences for community healthcare providers and the public.

OCPL produces materials on topics ranging from allergic and immunologic diseases, to AIDS and other sexually transmitted diseases, to potential illnesses caused by agents of bioterrorism. These materials include press releases, information sheets, and booklets, which are distributed to more than 10,000 people who contact the Institute from around the world each year. In addition, hundreds of thousands more download or request materials from the NIAID Web site (*www.niaid.nih.gov*), which is now visited 1.5 million times each month.

The NIAID Web site is a searchable site containing a wealth of information about NIAID's organization and research programs, as well as descriptions of NIAID's laboratories. The Extramural Information Center includes program announcements, contact information for key personnel, and many other items of interest to current and potential grantees and contractors.

OCPL has reprinted its very popular low-literacy booklets on tuberculosis (TB)—*Tuberculosis* and *Tuberculosis Infection*. Both are available in Spanish. OCPL staff also have updated and printed the booklet titled *Malaria*. Malaria, like TB and HIV/AIDS, is a serious disease that kills millions of people worldwide. OCPL has distributed thousands of copies of the previous edition of *Malaria* to researchers and healthcare providers around the world. All publications also are available on the NIAID Web site.

A new OCPL communications initiative expands NIAID's efforts to keep more than 400 voluntary and scientific organizations updated about Institute activities. Periodic e-mails provide timely news on NIAID research advances that relate to the specific research interests of the organizations. In addition, OCPL disseminates news from the NIH Offices of Public Liaison, which include NIAID.

Exhibiting at scientific and health-related meetings is a key element of OCPL's outreach efforts. Institute staff distribute materials and answer questions about NIAID research and job opportunities at conferences, including the American Academy of Allergy, Asthma and Immunology; the American Society for Microbiology; the National Conference on Blacks in Higher Education; the Hispanic Association of Colleges and Universities; the American Public Health Association; and the Congressional Black Caucus. OCPL has been involved extensively in the outreach efforts of NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC). VRC is the first facility at the NIH dedicated solely to vaccine research and production. To help the Center recruit for HIV vaccine trials, OCPL is helping to construct community partnerships by targeting local news media, visiting local churches and other community organizations,

and attending HIV/AIDS-related conferences and meetings.

The NIAID Division of AIDS (DAIDS) is conducting a national HIV vaccine communications campaign to foster a better public awareness of HIV vaccine research. The campaign is designed to create a public dialogue to help the public better understand the research, support it, and support those who may volunteer for clinical trials. The Institute implemented a qualitative comprehensive research effort, including both primary research (for example, 28 focus groups representing communities most affected by HIV/AIDS) and secondary, or existing, research. Staff used the findings to plan and target the campaign strategy and message development.

A key component for the first year of the campaign was to engage "early adopters," those individuals and organizations that represent target audiences and are currently involved in HIV/AIDS prevention and treatment efforts. Roundtable discussions were held with leaders in the African-American and Hispanic communities to refine strategies and to engage participants in ongoing activities, such as materials development and outreach.

In coordination with NIAID's HIV Vaccine Trials Network, DAIDS implemented an advertising campaign targeting opinion leaders, especially in communities most affected by HIV/AIDS, along with a substantial print and broadcast outreach that publicly reveals key messages about HIV vaccine research. Workshops on HIV vaccine research were featured at scientific conferences, including the Conference on Retroviruses and Opportunistic Infections.

RESEARCH PLANNING

NIAID has a long-standing tradition of rigorous and prospective research planning, involving the development and prioritization of specific research initiatives on an annual basis and long-range, strategic planning. NIAID's planning process was cited as a model by the Institute of Medicine in its 1998 report titled *Scientific Opportunities and Public Health Needs: Improving Priority Setting at the National Institutes of Health.* The two pillars of this research planning process are the annual Winter Program Review (WPR) and the Summer Policy Retreat (SPR).

Program Reviews

NIAID's annual program reviews provide an opportunity to focus on future research opportunities and to review proposed research initiatives for new and ongoing research programs.

The specific objectives of the annual program reviews follow:

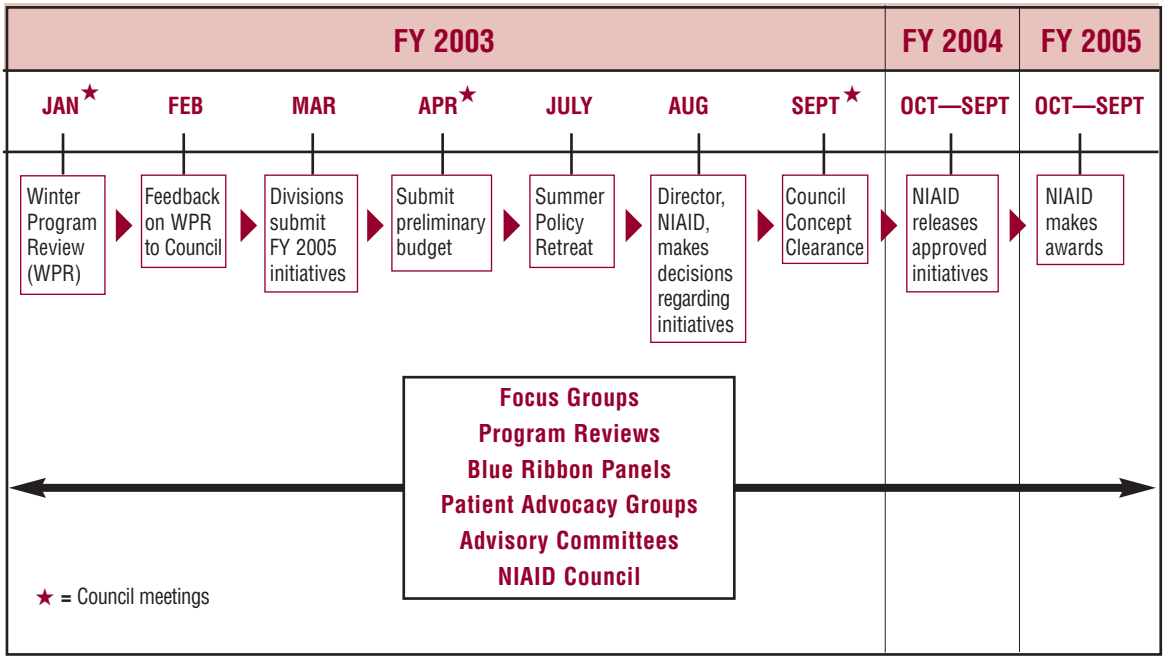
- Identify major public health, scientific, legislative, and budget directions that will influence NIAID programs;
- Discuss the scientific framework for and priority of new and ongoing research programs in the context of the above factors; and
- Use this information to make decisions about research activities and initiatives to be implemented in the future budget year.

Policy Retreats

The planning process is further enriched through annual policy retreats that provide opportunities for the following:

- Focus on broad scientific issues, opportunities, gaps, and directions;
- Identify the basis for scientific opportunities and gaps;

NIAID PRIORITY-SETTING PROCESS



- Ensure that scientific planning addresses the interests and priorities of the Congress, the Administration, the Department of Health and Human Services (DHHS), and the NIH Director;
- Propose approaches for responding to newly identified opportunities and needs;
- Identify the implications of changes in scientific or programmatic direction; and
- Prioritize newly identified opportunities and needs within the future budget year.

Throughout the year, NIAID convenes scientific workshops, blue ribbon panels, and program reviews to evaluate progress and to determine future needs and opportunities for the many diseases and areas of research within the Institute's purview. The NIAID Director and each research division consult extensively with NIAID stakeholders, including scientific experts, professional societies, and patient advocacy groups, to develop long-range, strategic plans as well as specific research initiatives. Areas of emphasis articulated in strategic plans, as well as those identified by DHHS, the NIH, Congress, the White House, and others, also help shape the Institute's decisionmaking and priority-setting process for new and continuing research programs.

Planning for future research initiatives is a multistep process that begins 2 years in advance of the projected implementation date. At each step in the process, the concepts for research initiatives are reviewed and refined. Concepts are first subjected to internal discussion during the annual program review, followed by a second level of review and clearance by the National Advisory Allergy and Infectious Diseases Council. Approved concepts are then developed by NIAID staff into various forms of grant and contract solicitations and announced to the scientific community. Proposed research projects are then peer reviewed and awarded on the basis of scientific merit, program relevance, and need.

Strategic Planning

NIAID's comprehensive strategic plan, *NIAID: Planning for the 21st Century,* is the product of an intensive effort that included a task force of national experts. The plan describes broad-based priorities to guide NIAID programs, policies, and initiatives through the next 3 to 5 years. The cornerstones of the plan are (1) immune-mediated diseases; (2) human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); (3) emerging infectious diseases and global health; and (4) vaccines. The full text of the plan can be accessed at *www.niaid.nih.gov/strategicplan.*

The Institute's guiding principles for global health research are articulated in the *NIAID Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis.* This plan identifies short-term, intermediate, and long-term research goals to address these devastating international killers. The plan can be accessed at *www.niaid.nih.gov/publications/globalplan.htm.*

Since the anthrax mail attacks of 2001, biodefense research has become a major component of NIAID's mission. The vigorous growth of the NIAID biodefense program is guided by expert recommendations and an intricate strategic planning process. In 2002, NIAID convened the first Blue Ribbon Panel

on Bioterrorism and Its Implications for Biomedical Research to assist in developing the *NIAID Strategic Plan for Biodefense Research*, the *NIAID Biodefense Research Agenda for Category A Agents*, and the *NIAID Biodefense Research Agenda for Category B and C Priority Pathogens.* The strategic plan emphasizes basic research on microbes, host defense mechanisms, and the development of drugs, vaccines, and diagnostics. The biodefense research agendas articulate immediate and longer term goals for research on Category A pathogens, which include smallpox, anthrax, Ebola virus, plague, botulinum toxin, tularemia, Marburg virus, Rift Valley fever, and Lassa virus, and goals for research on Category B and C priority pathogens. The agendas also address the research resources, facilities, and scientific manpower needed to conduct basic and applied research on these potential agents of bioterrorism. Both the strategic plan and the research agendas can be accessed at *www.niaid.nih.gov/publications/bioterrorism.htm.* Tremendous progress has been made since these reports were first released. NIAID has increased the breadth and depth of biodefense research and has made progress in meeting the specific goals of the Blue Ribbon Panel. The *NIAID Biodefense Research Agenda for CDC Category A Agents Progress Report* describes the progress made toward addressing the immediate goals outlined in the research agenda and can be accessed at *www.niaid.nih.gov/biodefense/research/category_A_Progress_Report.pdf.*

Another important strategic planning effort focuses on how to further stimulate research activities to address health disparities. The NIAID *Strategic Plan for Addressing Health Disparities* articulates specific action plans for reducing disparities through (1) research on HIV/AIDS, transplantation, autoimmune diseases, tuberculosis, hepatitis C virus, and sexually transmitted diseases; (2) support for research infrastructure and research training; and (3) support for community outreach projects. The full text of the health disparities strategic plan can be accessed at *www.niaid.nih.gov/healthdisparities/niaid_hd_plan_final.pdf.*

DIVISION OF ACQUIRED IMMUNODEFICIENCY SYNDROME

Mission

The Division of Acquired Immunodeficiency Syndrome (DAIDS) (*www.niaid.nih.gov/daids*) was formed in 1986 to develop and implement the national research agenda to address the HIV/AIDS epidemic. Specifically, the mission of DAIDS is to help ensure an end to the HIV/AIDS epidemic by increasing basic knowledge of the pathogenesis and transmission of the human immunodeficiency virus (HIV), supporting the development of therapies for HIV infection and its complications and co-infections, and supporting the development of vaccines and other prevention strategies. DAIDS accomplishes its mission through planning, implementing, managing, and evaluating programs in (1) fundamental basic research, (2) discovery and development of therapies and treatment strategies for HIV infection, its complications, and co-infections, and (3) discovery and development of vaccines, topical microbicides, and other prevention strategies.

To achieve its mission, DAIDS actively supports and promotes public and private-sector alliances to maximize available research opportunities and resources. By surveying developments in key research areas, DAIDS assesses ongoing needs in biomedical research as well as requirements for outreach activities and training scientific investigators. As part of this process, DAIDS works with advisory groups and community and health professional organizations, evaluating and redirecting program emphasis to respond to changing global research needs. DAIDS' commitment to advancing research worldwide has led to a steady increase in international activities, particularly in the developing world. This situation reflects the global impact of HIV/AIDS and the critical need for cost-effective prevention and treatment strategies in those limited-resource regions where more than 95 percent of HIV infections occur.

Scientific Areas of Focus

Basic Research

Basic research continues to increase our understanding of the biology of HIV and how the immune system responds to the virus. Knowledge gained from these studies enhances the ability of researchers to create new therapeutic agents and vaccines to combat HIV infection. DAIDS is studying the natural history of HIV progression in men and women through its cohort studies. The Women's Interagency HIV Study (WIHS) is a collaborative, multi-site longitudinal study designed to investigate the impact of HIV infection on women in the United States (*http://statepiaps.jhsph.edu/wihs*). The Multicenter AIDS Cohort Study (MACS) is an ongoing study of the natural history of HIV infection in homosexual men (*http://statepi.jhsph.edu/macs/macs.html*). MACS began in 1983 and was able to capture information on a large number of men who seroconverted while enrolled in the study. The Women and Infants Transmission Study (WITS) (*www.niaid.nih.gov/daids/wits.htm*) examines the natural history of HIV disease in the context of pregnancy, focusing on clinical, laboratory, and psychosocial aspects of maternal/infant transmission. WITS currently is investigating the long-term consequences of exposure to HIV and antiretrovirals in the children born during the study. Programs that study men and women separately give

researchers the ability to make gender-based comparisons, thereby adding value to the analyses.

DAIDS also supports a large portfolio of investigator-initiated grants in HIV pathogenesis in a variety of areas, including mechanisms of viral entry and infection; the structure, function, and mechanism of action of viral genes and proteins; the roles of cellular accessory molecules in replication; the immunologic and virologic events controlling primary infection and formation of the latent reservoirs; development of *in vitro* and *ex vivo* assays to monitor virus growth, immune responses, and reservoir status during HIV disease; animal models; and genetic analysis of host factors that modulate viral infection or disease progression. These grants serve as a source of new knowledge that fuels the discovery of new drugs and vaccine concepts.

To further stimulate the pursuit of new ideas, DAIDS funds a number of targeted programs, such as the Innovation Grants for AIDS Research Program, which provides limited funds for 2 years to help advance novel ideas that lack extensive preliminary data. The Novel HIV Therapies: Integrated Preclinical/Clinical Program is another example of how DAIDS supports the discovery, development, and evaluation of innovative HIV treatment concepts through multidisciplinary research and formal corporate partnering.

The Centers for AIDS Research (CFAR) program, also supported by DAIDS, provides administrative and resource support and emphasizes the importance of translational research and collaborations between basic and clinical investigators.

To assist the research community, NIAID supports the NIH AIDS Research and Reference Reagent Program, which is now in its 16th year of operation. The reagent program continues to provide the scientific community worldwide with a critical and unique resource for biologics and chemicals.

The Division's basic research efforts have yielded significant scientific information about the basic biology of HIV and the immune response to HIV infection. For example, DAIDS-funded investigators have identified the critical steps of how HIV uses the host machinery to enter and exit the cell, as well as the existence of multiple, persistent HIV reservoirs even with the use of highly active antiretroviral therapy (HAART). Although much has been learned in recent years, questions remain about the molecular interactions involved in the regulation of HIV expression and replication and about why the host immune response is not fully effective in controlling the infection. Information about how the virus attacks the body and how the body defends itself is critical to providing additional targets against which therapeutic interventions and vaccines can be directed.

Therapeutics

The Division's therapeutics research program supports the discovery and development of effective therapies for HIV/AIDS and associated complications and co-infections by facilitating and expediting research on highly promising candidate agents and novel therapeutic concepts. Through strategic planning and funding, DAIDS supports research on potential new cellular and viral therapeutic targets, enhanced formulations of existing agents, and treatment regimens to

improve adherence, minimize toxicities, and impede emergence of resistance. In addition, the Division supports research on approaches to restore the immune system, to protect uninfected cells, and to improve assays to measure pathogen load and host immunity. Investigations include basic research and drug discovery, preclinical development of candidate therapeutics including therapeutic vaccine research, and advanced clinical testing in humans. The evaluation of new drugs and therapeutic agents in people is a critical aspect of therapeutic research. These clinical studies define new agents that are effective against HIV and its associated complications and clarify how best to use these drugs. Human testing of anti-HIV therapeutics is carried out in three large DAIDS-sponsored clinical trials networks: the Adult AIDS Clinical Trials Group (AACTG) (*http://aactg.s-3.com*), the Pediatric AIDS Clinical Trials Group (PACTG) (*http://pactg.s-3.com*), and the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) (*www.cpcra.org*). In addition, research on acute HIV infection is conducted through the Acute HIV Infection and Early Disease Research Program (*http://aiedrp.org*). All of these DAIDS-supported clinical trials networks, especially the AACTG, are expanding their capabilities to conduct clinical trials in resource-poor developing countries. DAIDS also supports a large multicenter clinical trial titled Evaluation of Subcutaneous Proleukin in a Randomized International Trial (ESPRIT) to evaluate the effectiveness of interleukin-2 (IL-2) in maintaining immune function in addition to anti-HIV therapy and the impact of IL-2 on HIV disease progression.

DAIDS-sponsored therapeutics research has already had a dramatic impact on our understanding of the pathogenesis and clinical management of HIV infection over the past decade. Studies conducted by DAIDS-funded clinical trials research networks have (1) helped to define national and international guidelines for the treatment of primary HIV infection and associated opportunistic infections as well as prophylactic regimens for these secondary infections, (2) identified biological markers, such as CD4+ counts, and viral load for predicting a drug's effectiveness and disease progression, and (3) demonstrated the use of antiretroviral drugs for preventing mother-to-child transmission (MTCT) of HIV.

Studies have shown that HAART regimens, including reverse transcriptase and potent protease inhibitors, are capable of suppressing HIV viral load to undetectable levels in many infected individuals and partially restoring immune function. Such regimens have had a dramatic impact on HIV mortality in this country. Nonetheless, treatment failures occur as a result of the development of resistance to or noncompliance with these complicated and often toxic regimens. Moreover, damage to the immune system is incompletely reversed. To address these issues, DAIDS conducts studies of various treatment strategies in HIV-infected people with progressive disease and multidrug-resistant virus. For example, one study (CPCRA 064) evaluated the use of structured treatment interruption in this subset of HIV-infected individuals. In addition, there is an ongoing, urgent need for new therapeutic agents and regimens, new ways to boost immunity, and ways to rebuild and replace immunity lost to HIV infection. Toward that

end, DAIDS-funded research led to discovery of a therapeutic agent from a new class of anti-HIV drugs, known as fusion inhibitors, which was recently approved by the Food and Drug Administration. Early data suggest, however, that the development of resistance will continue to be a problem as new agents are introduced into HAART regimens, necessitating the need for continued research in this area.

Vaccine and Prevention Research

The development of safe and effective vaccine and nonvaccine strategies for the prevention of HIV infection and AIDS is a high priority of NIAID. DAIDS supports all phases of the discovery and development of preventive HIV vaccines, including basic research, preclinical testing, and human clinical testing of candidate HIV vaccines.

Vaccine research and development is supported through an extensive portfolio of investigator-initiated research in basic virology, immunology, and microbiology.

In addition, several DAIDS programs support the interface of preclinical and clinical research. These resources stimulate the development of new vaccine concepts and ensure a rational, deliberate process for moving concepts through to clinical trials. Among the vaccine research programs supported by DAIDS that encourage development along various stages of the vaccine pipeline are the Innovation Grants for Approaches in HIV Vaccine Research Program, which encourages novel and innovative concepts in vaccine discovery and development; the HIV Vaccine Research and Design Program (HIVRAD), which supports concepts that have evolved beyond early testing and "matured" innovation grants; and the Integrated Preclinical/Clinical AIDS Vaccine Development Program (IPCAVD), which supports the iterative processes of vaccine concept refinement and testing. Through this program, research groups investigate promising vaccine concepts that are amenable to product development and are likely to lead to preliminary studies in humans. In addition, HIV Vaccine Design and Development Teams (HVDDT), consisting of consortia of scientists from industry and/or academia, identify specific promising vaccine concepts amenable to targeted development.

Clinical evaluations in humans provide the only way of determining whether a vaccine candidate could trigger a safe and effective anti-HIV response in people. NIAID-supported clinical trials of preventive HIV vaccines are carried out in the HIV Vaccine Trials Network (HVTN) (*www.hvtn.org*). HVTN conducts all phases of clinical trials to determine the safety, immunogenicity, and efficacy of candidate preventive HIV vaccines. As HVTN concludes its fourth year, it has made progress towards its goal of developing and conducting a comprehensive HIV vaccine clinical research agenda that addresses the scientific and public health needs and builds on scientific opportunities in the field of HIV vaccine research. HVTN has undergone significant expansion to support international trials, instituted highly functioning protocol development teams, developed new vaccine concepts and advanced new protocols, reorganized laboratory programs, and developed an extensive training program. (Additional HVTN information is located in the Vaccine Research and Development

section of Selected Scientific Areas of Research on page 139.)

DAIDS also supports research on other biomedical and behavioral approaches to prevent the spread of HIV/AIDS. These approaches include drugs or vaccines that prevent MTCT of HIV, microbicides for preventing sexual transmission of HIV, interventions that reduce behaviors that expose people to HIV, programs to reduce intravenous drug abuse, measures to control other sexually transmitted diseases, and antiretroviral therapies to reduce the spread of HIV from infected people to their partners. NIAID-supported prevention clinical trials are centered in the HIV Prevention Trials Network (HPTN) (*www.hptn.org*). HPTN, formed in 2000 with additional support from the National Institute of Child Health and Human Development, the National Institute of Mental Health, and the National Institute on Drug Abuse, is a global, multicenter network dedicated to nonvaccine prevention research. Additional HPTN information is located in the AIDS section on page 42.

The Division's comprehensive vaccine and prevention program has led to a number of significant scientific advances in vaccine and prevention research. In the past, NIAID-supported researchers have improved the ability of vaccines to induce an antibody response by modifying the envelope protein, further explained the envelope structure of HIV, advanced our understanding of the role of cellular responses in controlling HIV, developed improved assays for measuring cytotoxic T lymphocytes, developed new and better animal models for testing candidate vaccines, and evaluated promising candidates in animal and clinical studies.

To accelerate identification of effective vaccine candidates, future studies will address the significance of latently infected resting T cells, study immune responses induced by current vaccine candidates, and assess the impact of HIV and human leukocyte antigen diversity. With regard to other prevention research, new microbicides will be evaluated for their safety and ability to prevent the sexual transmission of HIV. Moreover, building on past research that identified an inexpensive regimen to reduce HIV transmission at birth, NIAID will continue to evaluate other practical regimens for preventing MTCT of HIV, especially during breastfeeding.

Lastly, because the majority of new infections are occurring in the developing world, NIAID's prevention and treatment research activities are conducted on a global scale. In fiscal year 2001, NIAID launched the Comprehensive International Program of Research on AIDS (CIPRA). CIPRA provides long-term support directly to developing countries to plan and implement a comprehensive HIV/AIDS prevention and research agenda relevant to their populations and to strengthen the infrastructure required to carry out this research. As their national research capacity grows, countries can seek renewable CIPRA funding for multidisciplinary research projects and/or clinical trials for HIV prevention and/or treatment. In the past year, CIPRA awarded seven planning and organizational grants to Argentina, Brazil, Egypt, Georgia, Kenya, Malaysia, and Mozambique and one large multiproject grant to Senegal. For more information, visit the Web site at *www.niaid.nih.gov/daids/cipra*.

Major Programs and Networks

- Acute HIV Infection and Early Disease Research Program
- Adult AIDS Clinical Trials Group
- AIDS Research and Reference Reagent Program
- Centers for AIDS Research
- Comprehensive International Program of Research on AIDS
- HIV Prevention Trials Network
- HIV Vaccine Design and Development Teams
- HIV Vaccine Developmental Resources Contracts
- HIV Vaccine Research and Design Program
- HIV Vaccine Trials Network
- Innovation Grants for AIDS Research Program
- Innovation Grants for Approaches in HIV Vaccine Research Program
- Integrated Preclinical/Clinical AIDS Vaccine Development Program
- Integrated Preclinical/Clinical Program for HIV Topical Microbicides
- Laboratory Methods to Assess Responses to HIV Vaccine Candidates
- Liver and Pancreatic Disease in HIV Infection Program
- Microbicide Preclinical Development Program
- Multicenter AIDS Cohort Study
- National Cooperative Drug Discovery Groups—Opportunistic Infections
- New Technologies for HIV and HIV Vaccine-Related Research Program
- Novel HIV Therapies: Integrated Preclinical/Clinical Program
- Pediatric AIDS Clinical Trials Group
- Simian Vaccine Evaluation Units
- Terry Beirn Community Programs for Clinical Research on AIDS
- Therapeutics Research on AIDS-Associated Opportunistic Infections and Malignancies Program
- Women and Infants Transmission Study
- Women’s Interagency HIV Study

DIVISION OF ALLERGY, IMMUNOLOGY, AND TRANSPLANTATION

Mission

The human immune system is composed of intricate networks of specialized cells, molecules, and organs that act together to defend the body against foreign invaders, such as viruses, bacteria, and fungi, that may cause disease. However, aberrant immune responses play a critical role in the development of immune-mediated diseases, which include asthma and allergic diseases, autoimmune disorders, primary immunodeficiencies, and rejection of transplanted solid organs, tissues, and cells. Collectively, these chronic diseases affect tens of millions of Americans, resulting in considerable morbidity, mortality, pain and suffering, and high medical costs. Immune-mediated diseases cross many clinical specialties, and knowledge of the immune system and its role in disease is increasingly important in the clinical management of patients with these disorders.

The past two decades of focused research on the immune system have resulted in major advances in understanding the mechanisms that underlie a range of immune-mediated diseases. These advances in conceptual understanding now provide realistic opportunities for improvement in the diagnosis, treatment, and prevention of many of these diseases. The Division of Allergy, Immunology, and Transplantation (DAIT) (*www.niaid.nih.gov/research/dait.htm*) promotes and supports a broad range of research that seeks to further our understanding of the immune mechanisms underlying immune-mediated diseases and to translate this basic knowledge to clinical applications that will benefit individuals affected by these diseases. The ultimate goal of DAIT's research program is the development of effective approaches for the treatment and prevention of immune-mediated diseases.

The Division supports research initiated by individual investigators; multidisciplinary program projects that explore the mechanisms of immune-mediated diseases, transplantation immunology, and the basic biology of the immune system; clinical research programs to assess the safety and efficacy of new therapeutic approaches; and interdisciplinary cooperative research centers.

DAIT supports basic, preclinical, and clinical research to enhance our understanding of the causes of immune-mediated diseases and to apply this knowledge to the development of improved approaches to disease diagnosis, treatment, and prevention through demonstration and education research projects. DAIT evaluates the effectiveness of behavioral and educational interventions to promote health and prevent disease in defined populations.

DAIT's research programs are placing increasing emphasis on the preclinical and clinical development of new tolerogenic and immunomodulatory approaches for the treatment and prevention of transplant rejection, asthma and allergic diseases, and autoimmune diseases. Another area of program growth involves the application of emerging technologies to further our understanding of immunologic principles and to develop diagnostic and prognostic tools and biomarkers of disease activity and therapeutic effect.

Scientific Areas of Focus

Asthma and Allergic Diseases

Allergic diseases, including asthma, are among the major causes of illness and disability in the United States. Studies to examine the causes, pathogenesis, diagnosis, treatment, and prevention of allergic diseases represent a major focus of DAIT's basic and clinical research portfolio. DAIT's national network of Asthma and Allergic Diseases Research Centers focuses on the underlying immune mechanisms involved in these disorders and on approaches to improve diagnosis and treatment. In fiscal year (FY) 2002, DAIT established the Inner-City Asthma Consortium: Immunologic Approaches to Reduce Asthma Severity, a network of basic scientists and clinical investigators to evaluate the efficacy of promising immune-based therapies to reduce asthma severity and prevent disease onset in inner-city children.

Autoimmune Diseases

DAIT supports a broad range of basic and clinical research programs in autoimmunity. Basic research focuses on understanding the genetics of autoimmunity, elucidating the mechanisms of self-tolerance, developing approaches to induce self-tolerance, and characterizing pathways of immune-mediated tissue destruction. Knowledge gained from basic studies provides the rationale for developing clinical tests to diagnose autoimmune diseases and novel treatments for ongoing disease.

Basic and Clinical Immunology

The Division's basic immunology investigations focus on the properties, interactions, and functions of immune system cells and the substances produced by those cells. Information generated through this research provides the knowledge base necessary to develop treatment and prevention strategies. To promote research on these fundamental aspects of immune system functioning, DAIT supports multidisciplinary program projects on the biology of the immune system, including the basic biology of the immune responses for vaccine research, transplantation immunology and chronic rejection, and autoimmunity. Clinical immunology studies focus on immune-mediated diseases, including autoimmune diseases, asthma and allergic diseases, acute and chronic transplant rejection, and immunodeficiencies. Research in these clinical areas is supported by program projects on mucosal immunity, autoimmune diseases, and methods of immune intervention. In FY 2003, the Division recompeted and expanded the Autoimmunity Centers of Excellence program, which conducts clinical trials of new immune-based therapies for autoimmune diseases and basic research to understand the causes of these diseases. In addition, support is provided for research on the causes and underlying immune mechanisms of various inherited immunodeficiency diseases, such as severe combined immunodeficiency disease. In FY 2003, the Division funded the Primary Immunodeficiency Research Consortium, which will help prioritize and coordinate research directions and develop new resources for the study of these comparatively rare disorders.

Immune Tolerance

Immune tolerance is a high priority for NIAID, and, as part of a broad-based, long-range plan to accelerate research in this important area, DAIT established the Immune Tolerance Network (ITN). ITN is an international consortium of more than 80 investigators in the United States, Canada, and Europe dedicated to the clinical evaluation of novel, tolerance-inducing therapies in autoimmune diseases, asthma and allergic diseases, and rejection of transplanted organs, tissues, and cells. The goal of these therapies is to "re-educate" the immune system to eliminate injurious immune responses and graft rejection while preserving protective immunity against infectious agents. ITN also conducts integrated studies on the underlying mechanisms of these approaches and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in humans. More information about ITN is available on its Web site at *www.immunetolerance.org*.

Transplantation

The Division's research in transplantation immunobiology is focused on understanding the mechanisms whereby the immune system recognizes and either accepts or rejects transplanted organs, tissues, and cells; developing preclinical models to evaluate promising therapies to prevent and treat graft rejection; conducting clinical trials of new therapeutic agents and approaches to improve graft survival and function; and understanding the pathogenesis of chronic graft failure and developing new treatments and preventive strategies. Clinical research to evaluate new therapeutic approaches to improve kidney engraftment and survival is carried out through the Cooperative Clinical Trial in Pediatric Kidney Transplantation.

Primary Research Areas

Asthma and Allergic Diseases

- Asthma and Allergic Diseases Research Centers
- Inner-City Asthma Consortium

Autoimmune Diseases

- Autoimmune Diseases Prevention Centers
- Autoimmunity Centers of Excellence

Basic and Clinical Immunology

- Human Immunology Centers of Excellence
- Hyperaccelerated Award/Mechanisms in Immunomodulation Trials
- Vaccine Immunology Basic Research Centers

Immune Tolerance

- Immune Tolerance Network
- Innovative Grants on Immune Tolerance
- Non-Human Primate Immune Tolerance Cooperative Study Group

Transplantation

- Cooperative Clinical Trial in Pediatric Kidney Transplantation
- Immunopathogenesis of Chronic Graft Rejection

DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES

Mission

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV. DMID supports a wide variety of projects spanning the spectrum from basic research through applied research, along with the development and clinical evaluation of new drugs, vaccines, and diagnostics. NIAID also funds projects to sequence the full genomes of a number of medically important microbes, which can be exploited in many ways, for example, to trace microbial evolution, to locate targets for vaccine and drug development, and to identify mutations that contribute to drug resistance.

Research areas in basic bacteriology and mycology include molecular structure and function, genetics, biochemical composition, and physiologic and biochemical processes. Studies on these pathogens extend basic insights to identify vaccine candidate antigens and drug targets and to examine mechanisms of infection, pathogenicity, and virulence. Areas of particular interest include streptococci, pneumonia, nosocomial (hospital-acquired) infections, fungal infections, antibiotic resistance, bacterial sexually transmitted infections (STIs), and bacterial diarrheas.

Research areas in virology include molecular structure and function, genetics, synthesis, and reproduction of viruses; characterization of viral proteins and nucleic acids; mechanisms of pathogenicity, latency, persistence, and reactivation; interactions with immune systems; and vaccine development. Basic information is being used to combat important viral diseases such as influenza, herpes, congenital cytomegalovirus infection, hepatitis, and viral diarrheas.

Research on parasites involves the application of biochemical, genetic, and immunologic approaches. Studies of parasites are leading to the identification of protective and diagnostic antigens and to the development of more effective drugs. In addition, studies of arthropod vectors are aimed at controlling the transmission of important pathogens such as the malaria parasite.

One of the primary goals of the Division is to develop new and improved vaccines and strategies for vaccine delivery for the entire spectrum of infectious agents: bacteria, viruses, fungi, and parasites. Since 1981, DMID has supported a program for the accelerated development of new vaccines to direct advances in molecular biology, immunology, genetics, and epidemiology. An integral component of these efforts is vaccine safety, which is evaluated in every vaccine clinical trial sponsored by NIAID.

DMID also supports numerous efforts aimed at developing more effective diagnostic tools for infectious diseases. Examples include diagnostic tests for STIs and Lyme disease and the development of antimicrobial resistance markers.

Finally, DMID maintains a drug development program that supports research at three levels: drug discovery (accomplished by screening and by targeted molecular research), preclinical evaluation (in animal models of human infections), and clinical trials (evaluation of new therapies in humans).

Scientific Areas of Focus

Biodefense

As concern grows about the use of biological agents in acts of terrorism and war, Federal agencies are evaluating and accelerating measures to protect the public from the health consequences of such an attack. Our ability to detect and prevent infections that emerge as a result of bioterrorist incidents depends to a large degree on the state of biomedical science. Basic and applied research supported by the NIH complements the efforts of other Federal agencies by developing the essential tools—diagnostics, therapeutics, and vaccines—that are needed by physicians, nurses, epidemiologists, and other public health workers to prevent and control outbreaks of disease. NIAID is the primary NIH Institute that supports and conducts research on the diagnosis, prevention, and treatment of infections caused by a wide variety of emerging pathogens, including those that could be intentionally introduced.

In response to the need for rapid development of resources for biodefense, NIAID continues to expand its research related to potential agents of bioterrorism as part of a broad research agenda involving other agencies within the Department of Health and Human Services and the Department of Defense. The components of the NIH's biodefense research program include development of biodefense-relevant diagnostics, therapeutics, and vaccines, as well as genomics, basic research on potential agents of bioterrorism, and infrastructure to support advanced research. Recent programmatic accomplishments include expansion of the Vaccine and Treatment Evaluation Units (VTEUs) to accommodate testing of vaccines such as those for smallpox and anthrax; development of several new animal models for diseases caused by Category A, B, and C agents; many new initiatives to support grants and public-private partnerships for early product development through clinical trials of biodefense vaccines and drugs; and the recent award of the multimillion dollar Research Centers of Excellence (RCEs) and National and Regional Biocontainment Laboratories (NBLs and RBLs) across the United States, which will provide critical resources for biodefense and emerging infectious disease research.

Emerging and Re-emerging Infectious Diseases

Emerging infectious diseases include outbreaks of previously unknown diseases or known diseases whose incidence in humans has significantly increased in the past two decades. Re-emerging diseases are known diseases that have reappeared after a significant decline in incidence. Recent outbreaks of severe acute respiratory syndrome (SARS) in Asia and monkeypox in the United States are examples of emerging infectious diseases, whereas tuberculosis and pertussis are examples of diseases that have re-emerged after a period of decline. Factors involved in the emergence and re-emergence of infectious diseases include evolution of microbes, changes in vaccine compliance and use of antimicrobials, and changes in the interactions between humans and the environment due to human population growth, density, and contact with animal vectors or animals that may serve as disease reservoirs. Both emerging and re-emerging diseases have significant implications for domestic and global health. DMID, by supporting a broad

spectrum of research in infectious diseases, has the capacity to focus the research agenda to understand the epidemiology, pathogenesis, and microbiology of emerging infectious diseases and, ultimately, to develop mechanisms of control and prevention. Examples of DMID activities in this area include robust research programs in SARS, West Nile virus, Lyme disease, and influenza and the establishment in fiscal year 2003 of RCEs, NBLs, and RBLs across the United States, which will focus both on biodefense and emerging infectious diseases.

Vaccine Research and Development

DMID supports an active program of basic and applied research for the accelerated development of new vaccines, taking advantage of advances in molecular biology, immunology, genetics, and epidemiology. Research conducted under this program is contributing to the development of new vaccines for a wide variety of bacterial, viral, and parasitic diseases, including SARS, malaria, West Nile virus, herpes, and pneumococcal pneumonia. DMID also supports research to develop novel vaccine delivery methods, such as transcutaneous skin patches and nasal vaccines. One example of NIAID's success in developing innovative vaccines is the recent licensure by the Food and Drug Administration of the FluMist intranasal influenza vaccine, for which much of the research and early development was supported by NIAID. DMID also supports a large national and international network for clinical trials of safety and efficacy of vaccines. Recent expansions of the network will allow more trials focused on specific populations and larger clinical trials, including those for biodefense vaccines. DMID's *Jordan Report*, now in its 20th anniversary edition, is a unique resource developed by the Division to inform the public health community and the general public of recent developments and the state of the science in vaccine research. This report can be viewed online at *www.niaid.nih.gov/dmid/vaccines/jordan20*.

Antimicrobial Drug Resistance

Emergence of drug-resistant infectious agents is becoming an increasingly important public health concern. Rapid evolution of microbes and misuse of antibiotics are major contributors to the rising number of resistant pathogen strains. Tuberculosis (TB), gonorrhea, malaria, and childhood ear infections are just a few of the diseases that have become more difficult to treat because of the emergence of drug-resistant pathogens. Antimicrobial resistance is becoming a factor in virtually all hospital-acquired infections. Many physicians are concerned that several bacterial infections soon may be untreatable with currently available drugs.

NIAID funds a diverse portfolio of grants and contracts to study antimicrobial resistance in major viral, bacterial, fungal, and parasitic pathogens, including antimicrobial resistance among the major healthcare-associated bacterial pathogens. Specifically, NIAID supports investigator-initiated research on the molecular mechanisms responsible for drug resistance, as well as research to develop and evaluate new or improved therapeutics for disease intervention and prevention. Studies on several key organisms of interest seek to define how bacterial pathogens acquire, maintain, and transfer antibiotic-resistant genes. NIAID also continues to participate in an interagency task force for the development

of public health strategies for antimicrobial resistance. *The Public Health Action Plan to Combat Antimicrobial Resistance,* developed by the task force, describes issues, goals, and action items in surveillance, prevention and control, research, and product development, as well as a plan for interagency and industry coordination in addressing this critical health issue. The action plan is available online at *www.cdc.gov/drugresistance/actionplan/index.htm*.

Global Health

NIAID has developed a comprehensive global health research plan to address key issues in international health. Many of these activities focus on vaccine development. Genomics, microbial physiology, epidemiology and natural history, transmission/vector control, and development of improved diagnostics and therapies also are important areas of emphasis. Diseases of international health importance present additional scientific and logistical challenges, such as access to endemic sites and populations. The Institute supports field-based research through investigator-initiated grants, disease-specific initiatives, and special programs, such as the International Collaborations in Infectious Diseases Research and the Tropical Medicine Research Centers.

In 2001, NIAID published the *Global Health Research Plan for HIV/AIDS, Malaria, and Tuberculosis* in response to the tremendous burden of these three diseases on global health and the commitment to these diseases made by the United Nations and the Group of Eight nations (G8). (To view the plan, see *www.niaid.nih.gov/publications/globalhealth/global.pdf*.) The plan outlines NIAID's goals for fighting infectious diseases by building sustained research capability domestically and internationally and enhancing international partnerships. DMID supports a broad portfolio of research in both TB and malaria. Areas of emphasis in DMID's TB research include basic biology of the TB pathogen and drug-resistant strains, disease progression, diagnostics, vaccines, therapeutics, epidemiology, and genomics. The NIAID Tuberculosis Research Unit (TBRU) supports an international, multidisciplinary team of collaborators to translate basic research findings into clinical studies. Current research activities sponsored by NIAID for malaria include drug development, pathogenesis research, vaccine development, epidemiology, and vector control. In addition, in 2002, the completion of the genomic sequencing of both the malaria parasite and mosquito vector, which were supported by NIAID, signified an advance in knowledge about the disease that may lead to novel approaches to vaccines and antimalaria drugs.

Sexually Transmitted Infections

STIs are a critical global health priority for two reasons: their devastating impact on women and infants and their interrelationship with AIDS. Scientists now believe that people who have STIs are at an increased risk of contracting HIV/AIDS. DMID's STI research emphasis is on vaccine development and on clinical, epidemiologic, and behavioral investigations directed toward strategies for primary and secondary prevention of STIs and conditions associated with having STIs, for example, pelvic inflammatory disease, infertility, ectopic pregnancy, cervical cancer, fetal wastage, prematurity, congenital infection, and the spread of HIV. A public-

private partnership between NIAID and GlaxoSmithKline currently is supporting a phase III clinical trial for a new genital herpes vaccine in women that has the potential to prevent a disease that is estimated to affect 45 million people in the United States aged 12 years and older and that has significant health implications for infants. NIAID also supports a topical microbicide research effort to prevent STIs; this effort encompasses basic product development and clinical research.

Pathogen Genomics

In 1995, the first microbe-sequencing project, *Haemophilus influenzae* (a bacterium causing upper respiratory infection), was completed with a speed that stunned scientists. Encouraged by the success of this initial effort, researchers have continued to sequence an astonishing array of other medically important microbes. NIAID has made a significant investment in large-scale sequencing projects and includes projects to sequence the full genomes of many pathogens, including the bacteria that cause TB, gonorrhea, chlamydia, and cholera. In addition, NIAID collaborates with other funding agencies to sequence larger genomes of protozoan pathogens, such as the organism causing malaria.

The availability of microbial and human DNA sequencing has opened up new opportunities and allow scientists to examine functional analysis of genes and proteins in whole genomes and cells, as well as the host immune response and an individual's genetic susceptibility to pathogens. When scientists identify microbial genes that play a role in disease, drugs can be designed to block the activities controlled by those genes. Because most genes contain the instructions for making proteins, drugs can be designed to inhibit specific proteins or to use those proteins as candidates for vaccine testing. Genetic variations also can be used to study the spread of a virulent or drug-resistant form of a pathogen.

As a consequence of the Institute's increasing commitment to genomics activities, NIAID's Blue Ribbon Panel on Genomics has established a policy for support of large-scale genome-sequencing projects and includes priority organisms for large-scale sequencing projects. NIAID is committed to continuing its support to sequence the genomes of microbes as well as increasing its support for functional genomics, decoding sequence information, and determining its functional sequence. Moreover, NIAID is committed to facilitating the access and distribution of genomic resources and technologies to the research community for functional genomic analysis of microbial pathogens, as well as to supporting the development of bioinformatic and computational tools to allow investigators to store and manipulate sequence and functional data.

In summary, DMID supports a breadth of research activities on a variety of pathogens of importance in basic microbiology and infectious diseases.

DIVISION OF INTRAMURAL RESEARCH

Mission

Scientists in NIAID's Division of Intramural Research (DIR) (*www.niaid.nih.gov/dir*) conduct laboratory and clinical research covering a wide range of biomedical disciplines related to infectious diseases, immunology, and allergy. For example, DIR scientists conduct basic laboratory investigations to understand the biology and genetics of the viruses, bacteria, parasites, and fungi that cause infectious diseases. They also study the ticks, mosquitoes, fleas, and flies that transmit diseases such as West Nile fever, plague, and malaria. In addition, DIR has a large program focused on investigations of prion diseases, such as "mad cow" disease and chronic wasting disease of deer and elk, which are caused by a transmissible agent that has little in common with conventional infectious microbes.

Much of the research in DIR involves investigation of the multitude of interacting cells, antibodies, receptors, proteins, and chemicals that compose the immune system. A fundamental understanding of this intricate system is key to the development of therapies and vaccines for infectious diseases and critical to deciphering and treating immune system disorders—from mild allergies to life-threatening immunodeficiencies. The ultimate goal of the Division's research is to contribute to the development of new and improved therapies, diagnostics, and vaccines that will improve health, save lives, and enhance the quality of life in the United States and worldwide. This contribution may take the form of delineating a cell signaling pathway, discovering the function of a tick gene, determining the three-dimensional structure of an immune cell receptor, or finding the enzyme malfunction causing a primary immunodeficiency.

Translating laboratory research findings to the clinical arena is accomplished through the facilities of the Warren Grant Magnuson Clinical Center on the NIH campus. There, physician-scientists treat patients with a variety of diseases, including AIDS, vasculitis, immunodeficiencies, host defense defects, unusual fungal infections, asthma, allergies, various parasitic diseases, and disorders of inflammation. NIAID currently has more than 80 active clinical protocols under which patients participate in studies of new and promising treatments or diagnostic procedures, often derived from ongoing laboratory research efforts.

In addition to conducting innovative scientific studies, DIR researchers devote considerable effort to mentoring young scientists, teaching, and other academic pursuits. Each year, DIR laboratories host hundreds of predoctoral and postdoctoral trainees who are immersed in the superb scientific setting at the NIH while they participate in DIR's basic and clinical research programs.

The Division and its staff of scientists and physicians have received national and international recognition for their outstanding research achievements. Eight members of the current staff have been elected to the National Academy of Sciences, and many staff members have earned prestigious awards for their contributions to science.

Scientific Resources

Each of the 16 DIR laboratories (*www.niaid.nih.gov/dir/labs.htm*) has project-specific resources that are augmented by the expertise and services provided to all DIR labs by supporting branches. The DIR branches offer access to state-of-the-art technologies for peptide synthesis, protein sequencing, mass spectroscopy analysis of peptides and small molecules, electron microscopy, confocal microscopy, flow cytometry and cell sorting, and DNA microarray. The branches also provide genetically modified (transgenic as well as knockout/knockin) mice, extensive in-house animal breeding and holding facilities (including nonhuman primate), oversight of animal protocols, and support to scientists conducting animal studies. Animal care facilities, including biosafety level 3 facilities, are maintained in Bethesda, Maryland, and at DIR laboratories in Hamilton, Montana. In addition to the facilities directly managed by NIAID, DIR investigators have access to NIH-wide facilities such as the Mouse Imaging Facility. Investigators wishing to interact directly with other scientists in a very focused setting can do so by joining one of the more than 80 NIH scientific interest groups organized around specialty areas.

Computer linkages for DIR scientists consist of a local area network within NIAID and a wide area network linking DIR scientists to other areas of the NIH, such as the computer facilities of the NIH Division of Computer Research and Technology. The computer network also provides quick access to the libraries of the NIH Clinical Center and to the National Library of Medicine and links DIR researchers in the Maryland locations of Bethesda, Rockville, and the Frederick Cancer Research and Development Center and in the Rocky Mountain Laboratories in Hamilton, Montana. Teleconferencing equipment further enhances communications between DIR staff members and their colleagues across the campus and around the world. In addition, DIR investigators communicate with colleagues at the Malaria Research and Training Center in Mali via direct satellite uplinks, which are much faster and more dependable than the local Internet service provider connections.

Scientific Areas of Focus

Immunology Research

Immunology research is inextricably linked to studies of infectious diseases and allergy. In studying immunologic diseases, DIR scientists consider both the normal processes of the immune system and how these processes malfunction in the disease state. Findings from the studies are used in several ways. First, they are used in the development of new or improved vaccines that stimulate the immune system to recognize and destroy invading organisms. Second, the findings enhance the understanding and development of effective treatments for immunodeficiency diseases in which the immune cells are lacking or performing inadequately. Finally, they can be used in the elucidation and treatment of autoimmune diseases in which the immune cells attack the body's own cells. Current investigations include the following:

- Structural analysis of T cell and NK-cell receptors;
- Innate immune response to pathogenic bacteria;
- A mouse model of autoimmune disease; and
- Gene therapy for immunodeficiencies.

Allergy Research

Researchers studying allergic diseases concentrate on asthma; allergic reactions involving the skin, nasal passages, and sinuses; and chronic food allergy. Much of this research focuses on the mast cell, which plays an important role in many allergic disorders and secretes chemicals such as histamine. Histamine is responsible, in part, for triggering the events that cause the visible signs of an allergic reaction, such as hives, difficulty breathing, or a runny nose. Intramural scientists study how mast cells develop, their gene regulation, and their interactions with other cells in the connective tissue. Other projects are concerned with mucous membrane functions in the respiratory tract, both in normal and allergic individuals, and the role of the autonomic nervous system in causing allergic symptoms. Studies include the following:

- Cytokine profiles of allergic diseases;
- Tolerance studies for asthma;
- Development of mast cell lines for use in drug discovery; and
- Pathogenesis of food allergy.

Infectious Disease Research

DIR programs to improve the treatment and control of infectious diseases involve a multidisciplinary approach aimed at increasing our understanding of pathogenic organisms, the host response to infection, vector biology, and chemotherapeutics. Studies of the microorganisms—the bacteria, viruses, fungi, and parasites that cause diseases as varied as tuberculosis, AIDS, West Nile fever, and malaria—may reveal opportunities to use drugs to interfere with vital processes within the organism that are necessary for reproduction. Host studies may define the necessary immune response to successfully fight infection and help investigators design effective vaccines, whereas vector studies may reveal new targets for public health interventions. Application of this multidisciplinary approach to investigations of new and re-emerging infectious diseases and biodefense studies is a top DIR priority. DIR scientists are collaborating with colleagues from government, academia, and industry to develop vaccines, diagnostics, and therapeutics for high-priority pathogens and to conduct the basic laboratory research that provides the foundation for product development. Additional information about DIR studies of biodefense research and emerging infectious diseases can be found on pages 57 and 77, respectively. Other ongoing projects in DIR include the following:

- Structured therapy interruption as an AIDS treatment strategy;
- Development of more effective drugs for tuberculosis;
- Pathogenesis and cross-species transmissibility of prion diseases or transmissible spongiform encephalopathies; and
- Genetics of drug resistance, antigenic variation, and disease severity in malaria.

Vaccine Research

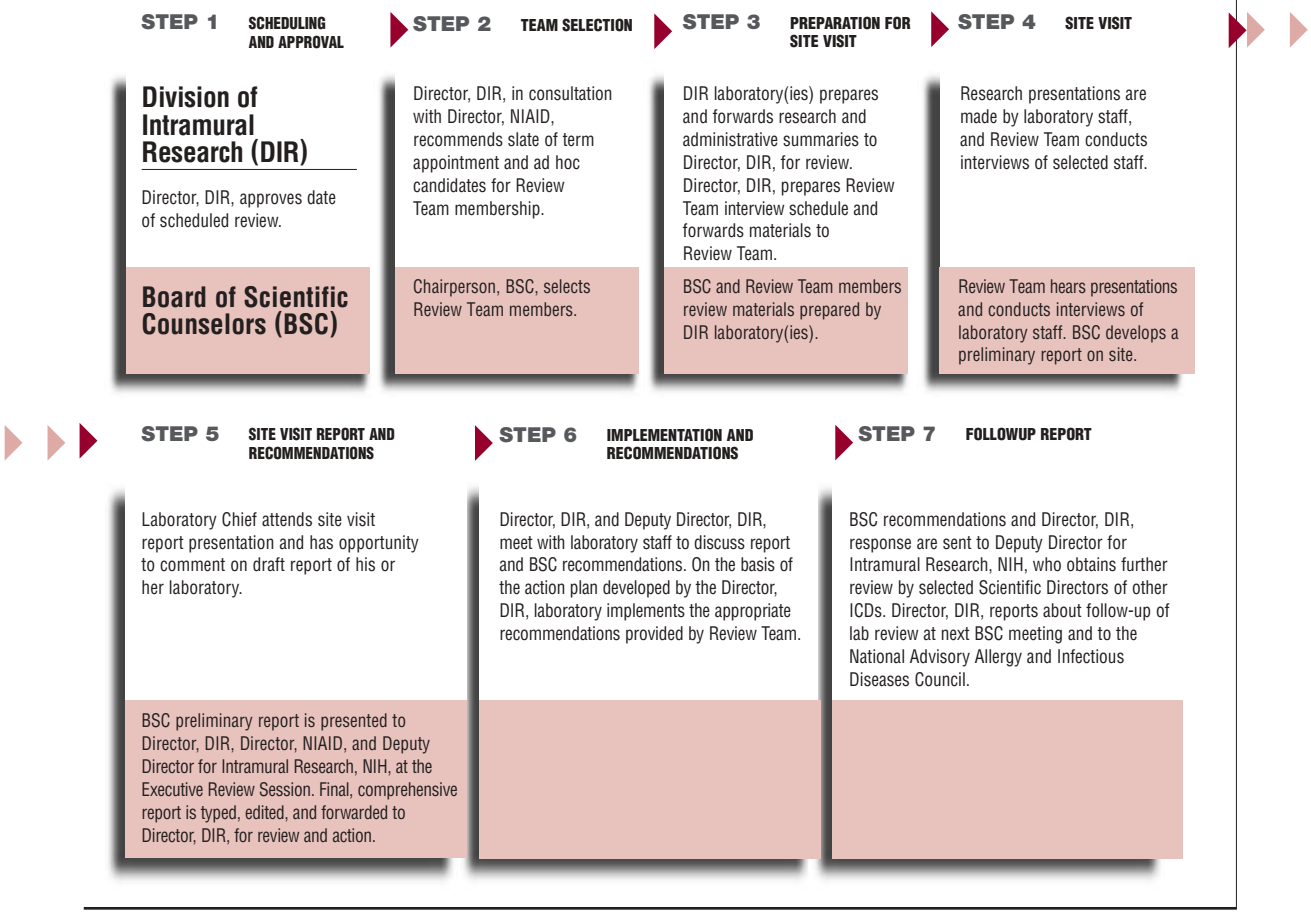
Candidate vaccines against many infectious agents of public health importance are undergoing laboratory and clinical testing in DIR. These include vaccines for respiratory and gastrointestinal viruses, hepatitis viruses, and infectious agents that cause common tropical diseases such as malaria and dengue. DIR scientists also are collaborating in the

development of vaccines to prevent the natural or deliberate spread of infectious diseases such as smallpox, severe acute respiratory syndrome (SARS), plague, and pandemic influenza. Studies are under way to develop vaccines against pathogenic flaviviruses, such as the West Nile virus, St. Louis encephalitis virus, and tick-borne encephalitis virus. Investigations continue toward the development of a vaccine against the respiratory syncytial virus, the principal cause of respiratory disease in infants in the United States and the world. In addition, the parainfluenza viruses, which cause respiratory disease in children and adults, are targets for vaccine development in DIR. (See page 139 for additional information.)

Laboratory Review Process

The following chart provides information on DIR's laboratory review process:

DIVISION OF INTRAMURAL RESEARCH LABORATORY REVIEW PROCESS



DALE AND BETTY BUMPERS VACCINE RESEARCH CENTER

Mission

The Dale and Betty Bumpers Vaccine Research Center (VRC) (*www.vrc.nih.gov*) is dedicated to translating the latest knowledge of disease pathogenesis and immunology into new vaccine strategies, thereby providing safe and effective means to prevent and control human diseases. The primary focus of VRC is to conduct research to develop an effective AIDS vaccine. The global epidemic of HIV infection is one of the most significant infectious disease threats to human health. Although new AIDS diagnoses and deaths have fallen significantly in many developed countries, the HIV/AIDS epidemic continues to accelerate in the developing world. There are an estimated 5 million new HIV infections each year, and, in 2003, the disease resulted in an estimated 3 million deaths.[1] Beyond the human tragedy of HIV/AIDS, the epidemic poses a significant impediment to the economic growth and political stability of many countries. In developing countries and in segments of the U.S. population, anti-HIV therapies are frequently beyond financial reach. Therefore, effective, low-cost tools for HIV prevention are urgently needed to bring the HIV epidemic under control. A globally effective, accessible vaccine remains the best hope for ending the HIV epidemic.

To combat HIV, we now have at our disposal new information about the molecular and immunologic basis of disease and improved tools for analysis of virus structure and measurement of immune responses. This scientific knowledge forms the basis for new ideas that may lead to novel strategies for effective vaccination. In addition, the scientific and industrial infrastructure has advanced to facilitate production and evaluation of vaccines. Nonetheless, the process of moving vaccine concepts through preclinical development and into initial clinical trials can be slow and unpredictable. Years of investment and research are required to progress through initial vaccine research, preclinical testing, and development to achieve an effective vaccine. In this setting, VRC has a unique opportunity and responsibility to facilitate the transition of new concepts in microbial pathogenesis, mechanisms of immunity, and vaccine design into clinical applications.

HIV strains worldwide display tremendous genetic diversity that may limit the protective immunity elicited by a single vaccine. Two types of HIV can be distinguished: these have been termed HIV-1 and HIV-2. HIV-2 is endemic in West Africa but is rare outside the region, whereas HIV-1 is the cause of the global pandemic. HIV-1 is classified into distinct genetic subtypes, or clades. For reasons that are not clear, these subtypes have distinct geographic distributions. To be effective, an HIV vaccine, or vaccines, will have to elicit immune responses against diverse strains of HIV-1. Also, because HIV attacks the primary cells of the immune system, persistent infection fails to produce effective immunity in a large percentage of the population. We are just beginning to understand how the virus evades immunologic surveillance to cause persistent infection and disease.

Development of an effective vaccine against HIV is the primary mission of VRC. To this end, VRC collaborates closely with the NIAID Division of AIDS (DAIDS), particularly with regard to regulatory support and to

implementation of clinical trials through established trial networks. In addition to its research program for HIV/AIDS, VRC's research programs in biodefense have been expanded, intensified, and accelerated. For example, VRC, working closely with the NIAID Division of Microbiology and Infectious Diseases (DMID) and with industry partners, is positioned to make substantive contributions in the development of vaccines protecting against Category A and B agents such as smallpox, West Nile virus, and hemorrhagic fever viruses (such as Ebola) posing a potential bioterrorist threat. VRC also is collaborating closely with DMID and with the NIAID Division of Intramural Research (DIR) to develop a vaccine for severe acute respiratory syndrome (SARS).

Scientific Areas of Focus

Historically, the process of vaccine development can be characterized as empiric, guided more by trial and error with inactivated or attenuated organisms than by rational design that builds on basic concepts in immunology and virology. Although this development process has been successful for numerous important infectious agents, many diseases remain for which no vaccine exists. A new science of vaccinology is now emerging that takes advantage of the latest technologies and scientific knowledge to design effective vaccine strategies. This process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. The VRC strategic plan is predicated on the belief that development of an effective AIDS vaccine will benefit from a thorough understanding of the basis of protective immunity to the virus and the mechanisms by which HIV evades immune surveillance. By having diverse components of vaccine research, development, production, and evaluation readily accessible at one site, along with a group of committed investigators with diverse skills but a common goal, VRC has embarked on a comprehensive and systematic approach to vaccine development.

The VRC process of rational vaccine design is closely coordinated with evaluation of vaccine candidates in animal models and human clinical trials. By embracing new discoveries and using them for the rational design of experimental vaccines, an iterative process of vaccine development, in which clinical evaluation informs basic research, is being established. The science of vaccinology is by its nature interdisciplinary, combining basic and applied research in immunology, virology, disease pathogenesis, molecular biology, and structural biology with clinical trials methodology. By encompassing these activities at a single center possessing the capacity for vaccine production, VRC hopes to advance the science of vaccine development.

The same infrastructure being employed to develop an effective HIV vaccine also is being deployed in the search for an improved smallpox vaccine and for effective vaccines against Ebola, West Nile virus, and SARS.

Research Goals and Objectives

VRC has four broadly encompassing research goals, each of which has multiple subparts. The goals are as follows:

- Goal 1: Scientifically design and develop effective vaccine candidates
  - Use knowledge of the HIV envelope structure to design immunogens that elicit potent virus-neutralizing antibodies

through a program of rational structure-based design and screening of immunogens

- Develop and optimize gene-based vaccine platforms that elicit broad and potent cell-mediated and humoral immunity

- Use state-of-the-art methods in genomics and bioinformatics to advance vaccine development

• Goal 2: Evaluate and optimize the immune response generated by candidate vaccines

- Identify and develop validated, reproducible methods to quantitate vaccine-induced immune responses in humans and primates

- Identify vaccine candidates and immunization strategies that enhance potency, antigen presentation, and immunogenicity

- Develop rational use of the primate model to assess vaccine strategies and define immune correlates

• Goal 3: Advance the most promising vaccine candidates into human clinical trials

- Develop the infrastructure to produce and test vaccine products

- Conduct clinical evaluation of candidate vaccines

- Evaluate preventive vaccine candidates in clinical protocols of therapeutic immunization

• Goal 4: Create the necessary infrastructure for translating basic research to the clinical setting

- Establish a contractor-leased and -operated Vaccine Pilot Plant (VPP) as a high priority for VRC. VPP will manage production of multiple vaccine candidates originating from VRC. To achieve this objective, VPP will provide research and development services to the Vaccine Production Laboratory located on the Bethesda campus to assist in transferring new vaccine technology for pilot-scale production of clinical trial material. VPP will be designed as a leased pilot plant in Frederick, Maryland, with an anticipated completion date of late 2004. Vaccines produced at VPP will support phase I and II clinical trials. In addition, the facility will incorporate design features that will allow conversion to larger scale operations capable of supporting phase III trials, if necessary.

Basic Research

Acquired Immunodeficiency Syndrome

VRC aims to develop vaccine candidates that will induce effective humoral responses (immune protection offered by antibodies) and cellular immune responses (immune protection offered by direct action of immune system cells). Data from several animal model systems strongly suggest that both humoral and cellular immunity play key roles in protection against HIV infection and disease. Based on the assumption that both cellular and humoral immunity are factors in preventing HIV infection or controlling HIV disease, the VRC preclinical research program explores basic science questions relevant to vaccine design. Guided by continuing research that reveals a better understanding of the basic elements of protective immunity, scientists at

VRC apply this knowledge toward the design of vaccines.

The VRC program in virus structural biology explores the rational design of vaccines that can induce potent virus-neutralizing antibodies. Using innovative crystallographic techniques, the structure of gp120, an important viral protein on HIV's surface, has been determined at the atomic level, leading to the identification and visualization of numerous overlapping mechanisms of immune evasion. VRC is using this and other structure-based analyses and protein-based principles to assist in the rational development of novel candidate vaccines for HIV. This approach also is being applied to the development of vaccines against other pathogenic viruses of public concern.

Development of candidate vaccines focuses on using portions of engineered HIV genes to express specific HIV proteins capable of triggering a protective immune response. These genes can be delivered using immunization with either DNA or viral vectors. In DNA immunization, the host is immunized by direct administration of viral genes. Viral vectors also can be constructed. These viral vectors transport one or more HIV genes and cause infected cells to produce HIV-specific proteins. Rodent and primate models can be used to evaluate safety, immunogenicity (induction of immune response), and degree of protection provided by these candidate vaccines. Such preclinical animal testing is closely integrated with VRC's basic science programs to provide information for iterative improvements in the development of new candidate vaccines.

A second major goal of the VRC basic research program is the evaluation and optimization of the immune response generated by candidate vaccines. The development of immunogens (substances causing an immune response) that elicit protective immunity against HIV is guided by studies that systematically evaluate the humoral and cellular immune responses generated by vaccine candidates. The development of reproducible, validated assays to measure T cell function and virus particle reduction are key to successful evaluation of both animal studies and human clinical trials. The VRC Immunology Core is currently designing, optimizing, and performing immunologic assays that measure the two major types of immune responses—cellular and humoral. Candidate vaccines are being evaluated by intracellular cytokine staining, ELISPOT assays, and measurements of neutralizing and binding antibodies. VRC also is expanding current assays to be applicable to more antigens and various clades of HIV as well as exploring ways to optimize and automate assay performance using state-of-the-art technologies in robotics.

Using these newly developing technologies, scientists can determine how effectively a candidate vaccine protects against infection or disease.

Ongoing preclinical studies in small animals and primates are evaluating vaccine dose, formulation, and delivery route and addressing the immunogenicity of multigene vectors and vaccine combinations. The accumulated knowledge from these preclinical studies will be used to develop vaccination strategies that induce optimal immune responses. Preclinical animal testing will be integrated closely with VRC basic science and clinical programs to provide information on the advancement of

promising candidate vaccines into human trials.

Ebola and Other Viral Hemorrhagic Fevers

Investigators at VRC, with scientific collaborators at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), have developed a potentially effective vaccine strategy for Ebola virus infection in nonhuman primates. Previous VRC studies have shown that a combination of DNA vaccination and boosting with adenoviral (ADV) vectors that encode viral proteins was protective against Ebola viral challenge and generated cellular and humoral immunity in cynomolgus macaques.

In addition to testing preventive vaccine candidates, VRC is currently testing a vaccine that may be useful in an acute outbreak setting. For example, a recently tested candidate (a single vector ADV-only) vaccine elicited protective immunity in monkeys after a 4-week postvaccination challenge, in contrast to previous 10-week or 6-month vaccine regimens. A second-generation product also will be evaluated that would provide coverage for Marburg and possibly Lassa virus.

VRC initiated a DNA product phase I trial for Ebola in October 2003.

West Nile Virus

VRC is currently developing a candidate vaccine for West Nile virus, a growing public health concern. The VRC candidate vaccine is gene based and uses DNA plasmids modified to increase expression of West Nile virus proteins. Preclinical immunogenicity studies are now under way. Further preclinical evaluation and viral challenge studies will be performed in the near future. VRC also plans to produce clinical-grade plasmid DNA for future phase I trials.

SARS

In response to the outbreak of the novel coronavirus implicated in SARS, VRC has initiated a new program to develop gene-based vaccines against this agent. Three parallel vaccine approaches are being pursued: plasmid DNA, recombinant adenoviral vectors, and a combination of these vectors, with proteins. Preclinical studies in laboratory animals will be conducted with these reagents to evaluate immunogenicity and to test protection against the SARS-associated coronavirus. At the same time, clinical grade (cGMP) production of these vectors will be initiated. Once produced, the vaccine vectors will be tested in phase I human clinical trials. Additional complementary studies also are being performed by VRC that will contribute to efforts to contain and treat this disease.

Clinical and Regulatory Infrastructure

VRC has assembled a full clinical research support team consisting of physicians, study coordinators, nurse practitioners, research nurses, and recruitment and outreach specialists. These staff represent VRC at community events, screen potential volunteers, and perform vaccinations and subsequent follow-up and testing of enrolled volunteers. VRC also has developed the strong regulatory infrastructure required to support the development and testing of vaccines. In collaboration with DAIDS and DMID, VRC staff manage the submission of Investigational New Drug (IND) applications to the Food and Drug Administration (FDA), develop protocols for human clinical trials, and ensure that all

studies are performed in accordance with FDA guidelines, while meeting all applicable reporting requirements.

Human Clinical Trials

A systematic, well-coordinated process of human vaccine trials is essential to effectively develop new vaccines. Although animal models are invaluable for guiding the development of vaccine approaches in general and are indispensable for evaluating efficacy and immune correlates of protection, parallel phase I and II studies in humans are required to validate safety and immunogenicity findings, and only human phase III efficacy trials can determine vaccine efficacy. To efficiently move vaccine development forward, VRC combines traditional empirical vaccine development with hypothesis-driven basic and preclinical research. This approach promotes an iterative process in which data from clinical evaluation will inform basic research and vaccine design, and findings in animal models will help prioritize approaches to test in clinical trials. In addition to traditional phase I studies in HIV seronegative volunteers, VRC has been studying the ability of vaccine candidates to augment native immunity in HIV-infected patients. Intensive evaluation of CD4 and CD8 immune responses will be correlated with control of viral replication and disease progression. In addition to the potential benefit to patients, studies of vaccine therapy will clarify mechanisms of cellular immunity and T cell memory that play a role in protection against HIV. Such data then can be applied to the development of therapeutic and preventive vaccines.

VRC actively collaborates with both intramural and extramural scientists and facilitates the movement of ideas from the broader community into clinical trials. Close ties are maintained with extramural investigators in the HIV Vaccine Trials Network (HVTN), where the infrastructure for conducting larger scale trials already is established. This collaboration will include efforts to develop vaccine candidates that can be evaluated at international field sites. When products emerge with real promise for licensure, VRC also will interact with the pharmaceutical industry, in which there is a large capacity for, and experience in, product development and distribution. Therefore, VRC is working to fill the gap between new basic concepts in immunology and initiation of clinical trials by applying state-of-the-art methods to rational vaccine design and evaluation at a single site.

In fall 2002, VRC initiated a phase I clinical trial to evaluate VRC-004, a global vaccine directed at the three most globally important HIV clades. The novel vaccine incorporates HIV genetic material from clades A, B, and C, which cause about 90 percent of all HIV infections around the world, and is the first multigene, multiclade HIV vaccine to enter human trials.

The trial vaccine is a DNA vaccine, a kind shown to be very safe in previous clinical trials. It incorporates parts of four HIV genes. Three of these vaccine components are modified versions of HIV genes called *gag*, *pol*, and *nef*, taken from clade B, the subtype that predominates in Europe and North America. The fourth vaccine component is derived from an HIV gene named *env*. The

env gene codes for a protein on the outer coat of the virus that allows it to recognize and attach to human cells. VRC scientists are the first to combine modified Env from clades A and C, which are the most common in Africa, as well as from clade B. A single vaccine combining multiple Env components from different HIV subtypes could, in theory, be effective in many places in the world. Expanded tests conducted through NIAID's HVTN are planned for several domestic sites as well as sites in Haiti and South Africa.

MVA

VRC currently is testing modified vaccinia Ankara (MVA) as an attenuated poxvirus with the potential to protect against vaccinia (the virus used to vaccinate against smallpox) or variola (the virus that causes smallpox). The vaccine was provided by Therion Biologics Corporation as part of a collaboration with VRC and DMID. Two phase I clinical trials are now under way testing MVA as a component of a safer smallpox vaccine in both vaccinia-naive and vaccinia-immune populations. VRC expects to complete its two current MVA/smallpox phase I trials in fiscal year (FY) 2004. Scientific collaborations have been developed with both DMID and private-sector partners for the development and production of MVA as a component of a safer smallpox vaccine for further clinical testing. Following the completion of the current phase I trials, further development of MVA as a component of a safer smallpox vaccine will be directed by DMID.

New Initiatives

VRC is planning new initiatives to support the growing needs of its expanding mission. VRC currently conducts phase I vaccine studies on the NIH Bethesda campus. In preparation for the conduct of phase II and III studies and to manage the complex activities related to international vaccine development, VRC is developing a team dedicated to advanced clinical development of candidate vaccines.

To further support research and development on vaccines for smallpox, Ebola, and West Nile virus, an additional laboratory dedicated to biodefense research is currently being formed, with the purpose of accelerating both basic research and subsequent development of biodefense-related vaccines.

Human Clinical Trials and Licensure of an AIDS Vaccine

VRC is working closely with its scientific collaborators and with FDA to discuss the potential for expedited approval of AIDS vaccines. The carefully considered use of surrogate end points (i.e., measures of the vaccine's ability to provoke an immune response) in AIDS vaccine trials could substantially accelerate the licensure of an effective AIDS vaccine. Clinical information validating the use of surrogate end points can accrue from well-designed trials, and this information can be applied to the design of future trials.

DIVISION OF EXTRAMURAL ACTIVITIES

Mission

The Division of Extramural Activities (DEA) (*www.niaid.nih.gov/ncn*) serves NIAID's extramural research community and the Institute in several key areas: overseeing policy and management for grants and contracts, managing NIAID's research training and international programs, and conducting initial peer review for funding mechanisms with Institute-specific needs. In addition to providing broad policy guidance to Institute management, DEA also oversees all of NIAID's chartered committees, including the National Advisory Allergy and Infectious Diseases Council (NAAIDC); disseminates information to its extramural community through its large Internet site; and develops extramural staff training and communications through the NIAID intranet. The Office of the Director, DEA, is a long-time leader in developing innovative technologies that have been adopted by the NIH, including electronic peer review and acquisition systems.

DEA staff members in every part of the organization interact intensively with grantees, contractors, reviewers, NAAIDC members, and applicants, as well as with staff of the other NIAID extramural divisions—the Division of Acquired Immunodeficiency Syndrome; the Division of Allergy, Immunology, and Transplantation; and the Division of Microbiology and Infectious Diseases.

DEA's Grants Management Branch issues all NIAID grant awards after negotiating the terms of the grant award with the applicant. Specialists in the Branch determine the amount of the award, develop the administrative terms and conditions, and release the official award document. They help clarify grant policies and procedures for investigators and answer their business and administrative questions, such as what costs are allowable and how to formulate a budget for a grant application. Grant specialists supervise the day-to-day administration and financial management of Institute grants and cooperative agreements, while ensuring that NIAID's grants are in compliance with existing policies. They are sources of valuable information on existing and new policies that may alter a grantee's requirements and privileges and that can inform grantees about which actions need approval and from whom.

Contract specialists manage the administrative aspects of NIAID's research and development contract portfolio. Toward those ends, they help develop requests for proposals, negotiate the technical and business aspects of proposals, and select the proposals. Working in DEA's Contract Management Branch (CMB), contract specialists are well versed in a full range of legal, technical, business, and cost-related topics, including Federal Acquisition Regulations and other policies and procedures. They provide investigators with guidance on changes in the scope of the research, the allowability of costs, and other administrative issues, including the use of contract funds, the technical or administrative performance of a contract, current or anticipated initiatives, and changes to a contract. More information about contracts is available at *www.niaid.nih.gov/contract*.

The Scientific Review Program (SRP) conducts peer review of NIAID's contract proposals and grant applications that address Institute-specific needs. These typically include program projects (P), cooperative agreements (U), training (T), and research career (K) grants, as well as applications responding to requests for applications and requests for proposals. Working in DEA's SRP, Institute review staff members assist investigators and NIAID staff members with issues related to grant and proposal preparation, including application format and documentation requirements. They also can provide insights into the peer review process and plans for specific review meetings; give advice on applying for a grant, including special review criteria and other requirements of NIAID program announcements, requests for applications, and requests for proposals; answer questions about the assignment or scheduling of applications or proposals for review; and advise applicants on NIH policy requirements. SRP manages NIAID's three chartered review committees and convenes special emphasis panels as needed.

DEA's Referral and Program Analysis Branch (RPAB) is the Institute's referral point for grant applications. RPAB also performs scientific classification and data analysis of all funded grants, contracts, and intramural research projects, including the categorization and analysis needed to generate official NIAID science-information reports.

Several offices and staff members in DEA's Office of the Director play specialized roles for the extramural community and the Institute. DEA staff members are a focal point for facilitating and coordinating several key activities, including small business programs (Small Business Innovation Research [SBIR] and Small Business Technology Transfer [STTR]), Academic Research Enhancement Award (AREA) grants, Council activities, and extramural communications. They develop policies and processes for NIAID's extramural research programs, including innovative electronic systems, and provide guidance on grant requirements and procedures to investigators.

The Office of Special Populations and Research Training (OSPRT) (*www.niaid.nih.gov/facts/mwhhp.htm*) oversees NIAID's portfolio of training grants, fellowships, and career development awards. Staff members in this Office answer questions from applicants about training-type support awards supported by NIAID. In addition, OSPRT administers the Research Supplements for the Underrepresented Minorities Program, which supports young minority scientists on NIAID-funded research grants.

The Office of International Extramural Activities (*www.niaid.nih.gov/ncn/grants/int/default.htm*) provides resources, help, and oversight for international applicants and grantees.

To keep the Institute's extramural research community informed and to provide advice on many research and policy topics, DEA produces the NIAID *Council News* newsletter and sponsors the *Council News* Extramural Information Center on the World Wide Web (*www.niaid.nih.gov/ncn*). These outreach resources keep grantees, applicants, and staff members up to date on Institute funding opportunities, policy changes, and other news. The site also educates the Institute's extramural constituency by providing budget and payline information; a series of tutorials on how the NIH functions, how to plan and write a grant

application, and how to manage a grant award; an online acquisition site for contracting; a glossary of NIH terms and acronyms; and a newsletter with policy updates and advice and articles on complex subjects, such as percentiling. Percentile is a ranking used by NIH Institutes to set grant paylines and make funding decisions. A percentile shows the relative position of each application's priority score among all scores assigned by a scientific review group at its last three meetings. The range is from 0.5 to 99.5; lower numbers represent better scores. For more information, go to the "Understanding Percentiles and Other Funding Factors" newsletter article (*www.niaid.nih.gov/ncn/budget/percentiles.htm*).

The Committee Management Office oversees the legal and policy requirements for NIAID's chartered committees, which include the NAAIDC, the Board of Scientific Counselors, the AIDS Research Advisory Committee, special emphasis panels, and three review committees.

The Office of Initiative Development, Data Quality, and Integrity coordinates and manages the planning, design, and review of extramural research initiatives and works to improve their timeliness and quality.